REMARKS

The Office Action dated December 28, 2006, has been received and reviewed.

Claims 1-27 are currently pending and under consideration in the above-referenced application, each standing rejected.

Claims 8, 9, and 11-13 have been canceled without prejudice or disclaimer.

New claims 28-35 have been added.

Reconsideration of the above-referenced application is respectfully requested

Rejections under 35 U.S.C. § 112, First Paragraph

Claims 1-27 stand rejected for assertedly failing to comply with the written description requirement of 35 U.S.C. § 112, first paragraph.

Independent claims 1, 15, 23, and 25-27 have been amended to include limitations that are expressed in "means-plus-function" language, including "means for assaying for enzymes or substrates," "means for detection," "first means for fluorescently labeling," and "second means for labeling."

"35 U.S.C. 112, sixth paragraph[,] states that a claim limitation expressed in means-plus-function language 'shall be construed to cover the corresponding structure... described in the specification and equivalents thereof.'" M.P.E.P. § 2181. With respect to means-plus-function limitations meeting the requirements of 35 U.S.C. § 112, first paragraph, "37 C.F.R. 1.75(d)(1) provides, in part, that 'the terms and phrases used in the claims must find clear support or antecedent basis in the description so that the meaning of the terms in the claims may be ascertainable by reference to the description.'" M.P.E.P. § 2181.

Various examples of means for assaying for "means for assaying for enzymes or substrates" are provided throughout the as-filed specification of the above-referenced application, including, without limitation, at page 8, lines 6-14; page 8, line 20, to page 9, line 4; page 10, line 15, to page 11, line 5; page 16, lines 6-19.

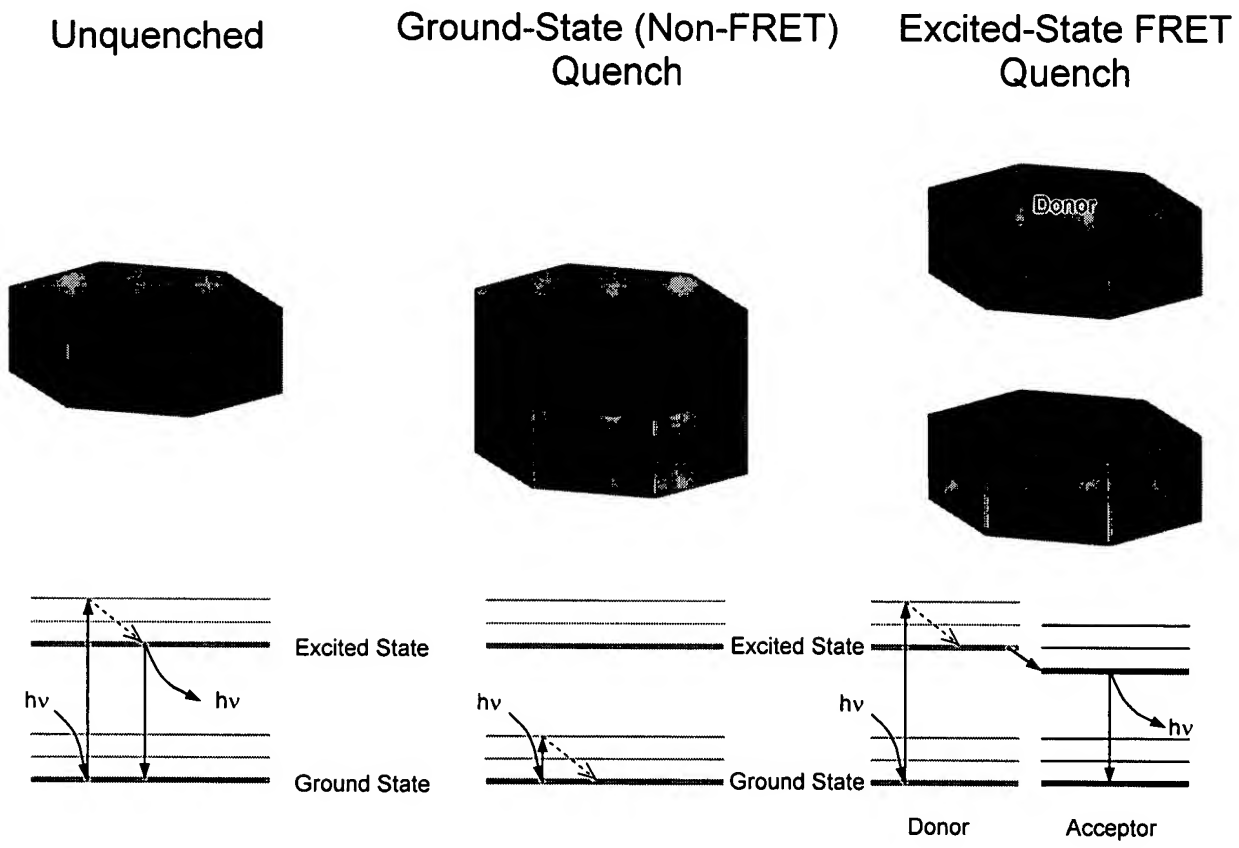
Non-limiting examples of "means for detection," "first means for fluorescent dye labeling" and "second means for dye labeling" appear throughout the as-filed specification in a number of locations, including at page 11, line 6, to page 12, line 9; page 17, lines 3-10.

It is, therefore, respectfully submitted that the specification of the above-referenced application provides an adequate written description of the subject matter recited in amended independent claims 1, 15, 23, and 25-27. Therefore, it is respectfully submitted that independent claims 1, 15, 23, and 25-27 comply with the requirements of both the sixth and first paragraphs of 35 U.S.C. § 112.

Accordingly, withdrawal of the 35 U.S.C. § 112, first paragraph, rejections of claims 1-27 is respectfully solicited.

Ground-State (Non-FRET) Quenching vs. Excited-State FRET Quenching

The following diagram is intended to show, by way of background and in very simple terms, the difference between non-FRET quenching and FRET quenching:



The diagram under the heading "Unquenched" represents unquenched fluorescence, in which a single fluorescent molecule is excited to a higher energy state (the excited state) by absorption of light (hv) of the appropriate energy. As shown by the graph beneath the single fluorescent molecule, from left to right, the fluorescent molecule is exposed to light (hv). Upon absorbing the light, the energy level of the fluorescent molecule increases, then decreases. Upon rapid decay of the fluorescent molecule's energy level to the lowest level of the excited state, the fluorescent molecule emits light (hv) (*i.e.,* it fluoresces).

The center diagram, which includes the heading "Ground-State (Non-FRET) Quench," depicts non-FRET quenching: The upper, fluorescent molecule is quenched in its ground state by direct contact with another, lower molecule. Although light is absorbed by the upper, fluorescent molecule, it cannot reach the excited state, and returns to its lowest ground state energy level without emitting any light, as shown in the center. This quench mechanism is a form of static quenching.

Excited-state FRET quenching differs from non-FRET quenching, as illustrated in the right diagram, which is labeled "Excited-State FRET Quench." As shown in the corresponding graph, the fluorescent molecule, which is labeled "Donor," absorbs light and reaches the excited state – in the same manner that occurs with an unquenched fluorescent molecule. If, however, a suitable "Acceptor" fluorescent molecule is within some critical distance, as shown, rather than energy in the form of light, energy from the "Donor" fluorescent molecule is transferred to the "Acceptor" fluorescent molecule. This energy transfer from "Donor" to "Acceptor" is non-radiative, resonance energy transfer (FRET). The energy transferred, and the degree of quenching is proportional to the sixth power of the distance between the donor and acceptor molecules. Energy transferred to the "Acceptor" is emitted by the "Acceptor" as light ("Acceptor" fluorescence emission). The closer the donor and acceptor are, the greater the quench of the "Donor" and the greater the emission of the "Acceptor."

Rejections under 35 U.S.C. § 102

Claims 1, 2, 5-7, 9, 11, 15, and 21 stand rejected under 35 U.S.C. § 102.

A claim is anticipated only if each and every element, as set forth in the claim, is found, either expressly or inherently described, in a single reference which qualifies as prior art under 35 U.S.C. § 102. *Verdegaal Brothers v. Union Oil Co. of California*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). The identical invention must be shown in as complete detail as is contained in the claim. *Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989).

Odom

Claims 1, 2, 5-7, 9, 11, 15, and 21 stand rejected under 35 U.S.C. § 102(b) for reciting subject matter which is purportedly anticipated by the subject matter described in bed in Odom, O.W., et al., "An apparent conformational change in $tRNA^{Phe}$ that is associated with the peptidyl transferase reaction," Biochemie 69:925-38 (1987) (hereinafter "Odom").

Independent claim 1 is drawn to a biomolecular substrate. The biomolecular substrate of independent claim 1, as amended and presented herein, includes a core molecular backbone and a means for detection. The means for detection includes a dissociatable, ground state-quenched intramolecular dimer. The dimer includes a first means for fluorescent labeling and a second mans for labeling. Upon covalent, non-cleaving modification of the biomolecular substrate, the second means for labeling dissociates from the first means for fluorescent labeling of the dimer, enabling the first means for fluorescent labeling to fluoresce.

Independent claim 15 has been amended to include the same limitations.

Odom describes a process in which fluorescent probes are covalently attached to *E. coli* $tRNA^{Phe}$ at position 47 (FITC) and at position 16 or 20 (DCCH). Page 931, second column. Odom does not, however, include any express or inherent description that the FITC and DCCH at these positions form an intramolecular dimer, as would be required for Odom to anticipate each and every element of independent claim 1 or independent claim 15.

Further, as previously described in abundant detail, the description of Odom is limited to FRET-quenching, whereas independent claims 1 and 15 are respectively drawn to biomolecular substrates and assay methods that employ non-FRET quenching.

Accordingly, it is respectfully submitted that, under 35 U.S.C. § 102(b), independent claims 1 and 15 are both allowable over the subject matter described in Odom.

Claims 2 and 5-7 are each allowable, among other reasons, for depending directly from independent claim 1, which is allowable.

Claims 9 and 11 have been canceled without prejudice or disclaimer, rendering moot the rejections of these claims.

Claim 21 is allowable, among other reasons, for depending directly from independent claim 1, which is allowable.

Gildea

Claims 1, 2, 5-7, 9, 11, 15, and 21 also stand rejected under 35 U.S.C. § 102(e) for being drawn to subject matter that is allegedly anticipated by the subject matter described in U.S. Patent 6,485,901 to Gildea et al. (hereinafter "Gildea").

Like Odom, Gildea also lacks any express or inherent description of a biomolecular substrate that includes means for detection with a dissociatable, ground state-quenched intramolecular dimer of first and second means for labeling. This is apparent in view of the Gildea's statements that "the fluorophore and quencher moieties of a Linear Beacon," which Gildea distinguishes from "Molecular Beacons," which require hairpin structures unique to nucleic acids (col. 7, lines 59-61), "are... situated to... achieve a degree of quenching which is fairly independent of probe length of nucleobase sequence" and, further, "that the noise and signal to noise ratio for Linear Beacons is substantially independent of length of subunits which separate donor and acceptor moieties, ionic strength of the environment or the presence or absence of magnesium." Col. 8, lines 36-40 and 51-54.

As such, it is apparent that Gildea does not anticipate each and every element of independent claim 1 or independent claim 15, as would be required to maintain the 35 U.S.C. § 103(a) rejections of these claims.

Claims 2 and 5-7 are each allowable, among other reasons, for depending directly from independent claim 1, which is allowable.

Claims 9 and 11 have been canceled without prejudice or disclaimer, rendering moot the rejections of these claims.

Claim 21 is allowable, among other reasons, for depending directly from independent claim 1, which is allowable.

It is respectfully requested that the 35 U.S.C. § 102 rejections of claims 1, 2, 5-7, 9, 11, 15, and 21 be withdrawn, and that each of these claims be allowed.

Rejections under 35 U.S.C. § 103(a)

Claims 1-27 have been rejected under 35 U.S.C. § 103(a).

The standard for establishing and maintaining a rejection under 35 U.S.C. § 103(a) is set forth in M.P.E.P. § 706.02(j), which provides:

> To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

Blumenthal, Odom, and Tyagi

Claims 1-27 are rejected under 35 U.S.C. § 103(a) for being directed to subject matter that is purportedly unpatentable over the subject matter taught in Blumenthal, D.K., "Development and Characterization of Fluorescently-Labeled Myosin Light Chain Kinase Calmodulin-Binding Domain Peptides," Molecular and Cellular Biochemistry, 1271128: 45-50 (1993) (hereinafter "Blumenthal"), in view of teachings from Odom, and, further, in view of the subject matter taught in WO 97/39008 and U.S. Patent 6,150,097 of to Tyagi (hereinafter "Tyagi").

Claims 8, 9, and 11-13 have been canceled without prejudice or disclaimer, rendering the rejections of these claims moot.

Blumenthal teaches biomolecular substrates that include a single dye (acrylodan) for measuring changes in the conformation of a calmodulin binding domain of a peptide when the peptide binds calmodulin. In one of the methods, the analyzed peptide included naturally occurring tryptophan residues and was employed as a FRET donor molecule, while the acrylodan acted as the FRET acceptor molecule. When **calmodulin binds noncovalently to the peptide** (*i.e.,* the peptide is not covalently modified), a conformational change in the peptide occurred, which decreased the distance between the tryptophan and the acrylodan and, thus, caused an increase in FRET quenching.

The teachings of Odom have been summarized above. Most notably, the teachings of Odom are limited to use of a dye pair in which changes in FRET quenching are indicative of conformational changes in $tRNA^{Phe}$ that may occur as a ribosome-bound AcPhe-tRNA is deacylated to produce a $tRNA^{Phe}$ by the peptidyl transferase reaction. Odom, p. 937, first column. During the peptidyl transferase reaction, **deacylation of the ribosome-bound AcPhe-tRNA involves the cleavage of covalent bonds**. First, the peptidyl-tRNA is cleaved from the carboxyl end of a growing peptide chain and then peptide bond formation proceeds with the aminoacyl-tRNA. The covalent bond cleavage occurs as a result of nucleophilic attack by the lone pair of electrons on the amino nitrogen of the aminoacyl-tRNA on the carbonyl carbon that attaches the growing polypeptide chain to the peptidyl-tRNA molecule in the P site of the ribosome. Like Blumenthal, Odom does not include any teaching or suggestion of use of non-FRET quenching to determine whether or not a biomolecular substrate has been modified or, more specifically, that non-FRET quenching may be used to determine when a biomolecular substrate has been covalently modified but not cleaved.

Tyagi teaches the use of "Molecular Beacon" oligonucleotide probes to monitor binding of oligonucleotide probes labeled with two fluorescent dyes or a fluorophore and a quencher to target sequences in nucleic acids. While fluorescence of the fluorophore may be quenched when the quencher "touches" the fluorophore and, thus, ground state quenching may occur, such quenching only occurs because a hairpin, which is ***unique to nucleic acids***, has been designed

into the nucleic acid. When **the nucleic acid binds** (by hydrogen bonding; *i.e.*, **noncovalently**) **to a complementary nucleic acid sequence**, the hairpin unwinds, causing dissociation of the dyes and, thus, allowing for fluorescence of the fluorophore.

It is respectfully submitted that the teachings of Blumenthal, Odom, and Tyagi do not support a *prima facie* case of obviousness against any of claims 1-27. In particular, it is respectfully submitted that Blumenthal, Odom, and Tyagi, taken in any combination or individually, do not teach or suggest each and every element of any of claims 1-27. More specifically, none of Blumenthal, Odom, or Tyagi, taken either together or separately, teaches or suggests a biomolecular substrate that is *covalently modified without being cleaved*, as recited by independent claim 1; a method in which a biomolecular substrate is *covalently modified without being cleaved*, as recited in independent claims 15, 25, and 27; or a kit including a biomolecular substrate and a dye that, when the biomolecular substrate is *covalently modified without being cleaved*, dissociates from another dye to reduce quenching by ground-state interactions between the dyes, as recited in independent claim 26.

Further, with respect to claims 23 and 24, it is respectfully submitted that independent claim 23 is allowable since none of Blumenthal, Odom, or Tyagi teaches or suggests a method for assaying protein kinase activity, let alone various aspects of such a method, including provision of a biomolecular substrate that includes a KID peptide sequence or a pair of molecules that, when the biomolecular substrate is not covalently modified, form an intermolecular dye dimer, but, when the biomolecular substrate is phosphorylated, dissociate to reduce quenching between the pair of molecules. Claim 24 is allowable, among other reasons, for depending directly from claim 23, which is allowable.

For these reasons, the teachings of Blumenthal, Odom, and Tyagi do not support a *prima facie* case of obviousness against any of claims 1-7, 10, or 14-27. Accordingly, it is respectfully submitted that, under 35 U.S.C. § 103(a), the subject matter recited in each of claims 1-7, 10, or 14-27 is allowable over the teachings of Blumenthal, Odom, and Tyagi.

Macala, McIlroy, Schultz, or Ventura in View of Blumenthal or Wei and Odom or Tyagi

Claims 1-27 stand rejected under 35 U.S.C. § 103(a) for reciting subject matter that is allegedly unpatentable over the subject matter taught in Macala, L.J., et al., "Measurement of cAMP-Dependent Protein Kinase Activity Using a Fluorescent-Labeled Kemptide," Kidney International, 54: 1746-50 (1998) (hereinafter "Macala"), McIlroy, B.K. et al., "A Continuous Fluorescence Assay for Protein Kinase C," Analytical Biochemistry, 195: 148-152 (1991) (hereinafter "McIlroy"), U.S. Patent 5,580,747 to Schultz et al. (hereinafter "Schultz"), or Ventura, C., et al., "Phorbol Ester Regulation of Opioid Peptide Gene Expression in Myocardial Cells," The Journal of Biological Chemistry, 270(50): 301 15-20 (1995) (hereinafter "Ventura"), in view of teachings from Blumenthal, or Wei et al., WO 98/50579 (hereinafter "Wei"), and the teachings of Odom or Tyagi.

Claims 8, 9, and 11-13 have been canceled without prejudice or disclaimer, rendering the rejections of these claims moot.

Macala teaches a protein kinase assay that uses a protein kinase substrate labeled with *one fluorophore*. The Macala assay includes electrophoretically separating the phosphorylated product from the nonphosphorylated fluorescent substrate using agarose gels. The Macala assay is not a homogenous assay that can be use for continuous, high throughput screening of enzyme activity, nor for use in measuring enzyme activity in living cells. As acknowledged by the Office, Macala does not teach or suggest a substrate having two dyes attached or a library of compounds.

Schultz teaches a fluorescent assay using a modified substrate labeled with a *single dye*. The Schultz assay requires the separation of the reaction products from the substrate by electrophoresis, chromatography, or extraction. Like Macala, this assay is not a homogenous assay that can be use for continuous, high throughput screening of enzyme activity, nor for use in measuring enzyme activity in living cells. As acknowledged by the Office, Schultz does not teach or suggest a substrate having two dyes attached or a library of compounds.

McIlroy and Ventura, likewise, teach a *single-labeled* fluorescent protein kinase peptide substrates. The single-labeled peptide shows a *20% decrease* in activity when it is fully phosphorylated. Because the fluorescence change is measured in a decrease with a maximum

change of 20%, it is difficult to measure low levels of phosphorylation. As acknowledged by the Office, neither McIlroy nor Ventura teaches or suggests a substrate having two dyes attached.

Blumenthal teaches biomolecular substrates that include a *single dye* (acrylodan) for measuring changes in the conformation of a calmodulin binding domain of a peptide when the peptide *noncovalently* binds calmodulin. When such noncovalent bonding occurs, a distance between the acrylodan and a tryptophan residue on the peptide decreases, resulting in an increase in FRET quenching.

The teachings of Wei are limited to a biological assay method in which an enzyme substrate is cleaved to separate two dies from a dimer. Likewise, the teachings of both Odom and Tyagi are limited to assays in which substrates are cleaved.

It is noted that the teachings of each of Macala, McIlroy, Schultz, Ventura, and Blumenthal are limited situations in which a single dye molecule is attached to an analyzed molecule. Thus, none of these references teaches or suggests a substrate that includes or a situation in which two means for labeling (*e.g.,* dyes) may physically associate with each other, as an intramolecular dimer or otherwise. It is also noted that none of Blumenthal, Wei, Odom, or Tyagi teaches or suggests covalent modification of a biomolecular substrate without cleaving the biomolecular substrate.

In view of the foregoing, it is respectfully submitted that, without the benefit of hindsight provided by the claims of the above-referenced application, one of ordinary skill in the art wouldn't have been motivated to apply teachings that are limited to cleavage of a molecule to reduce fluorescent quenching between two labels (Wei, Odom, and Tyagi) to situations in which a single fluorescent dye is used to assay non-cleavage changes to molecules (Macala, McIlroy, Schultz, Ventura, and Blumenthal).

It is, therefore, respectfully submitted that no combination of teachings from Macala, McIlroy, Schultz, Ventura, Blumenthal, Wei, Odom, and Tyagi could be relied upon to establish a *prima facie* case of obviousness against any of the claims of the above-referenced application.

Withdrawal of the 35 U.S.C. § 103(a) rejections of claims 1-27 is respectfully requested, as is the allowance of claims 1-7, 10, and 14-27.

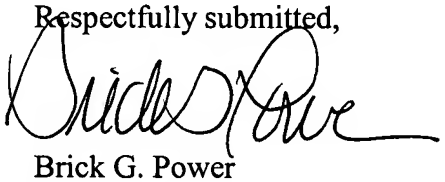
New Claims

New claims 28-35 have been added. Each of new claims 28-35 depends directly or indirectly from independent claim 1. It is respectfully submitted that none of new claims 28-35 introduces new matter into the above-referenced application, and that each of these claims is drawn to subject matter that is allowable over the art upon which the Office has relied in the currently outstanding rejections.

CONCLUSION

It is respectfully submitted that each of claims 1-7, 10, and 14-35 is allowable. An early notice of the allowability of each of these claims is respectfully solicited, as is an indication that the above-referenced application has been passed for issuance. If any issues preventing allowance of the above-referenced application remain which might be resolved by way of a telephone conference, the Office is kindly invited to contact the undersigned attorney.

Respectfully submitted,



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